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(54) Title: COMPOSITION, FOR THE TREATMENT OF ASTHMA, CONTAINING LORATADINE AND A DECONGESTANT

(57) Abstract

The invention encompasses a method for improving pulmonary function of a patient suffering from asthma, comprising administering to the patient customary rhinitis treatment-effective amounts of loratadine and a decongestant such as pseudoephedrine.

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COMPOSITION, FOR THE TREATMENT OF ASTHMA, CONTAINING LORATADINE AND A DECONGESTANT

INTRODUCTION TO THE INVENTION

The invention relates to methods for relieving symptoms of allergic diseases, and more particularly to relieving bronchial asthma symptoms.

Asthma is considered to be a very serious chronic allergic disorder, and is typically characterized by airway hyperresponsiveness, recurrent airflow obstruction and symptoms of cough, wheezing and breathlessness. It is one of the most common chronic diseases of childhood, perhaps affecting as many as ten percent of children. Asthma is economically very significant, as it causes considerable time loss from jobs and school, is one of the most common reasons for visits to the physician and is responsible for many admissions to emergency treatment facilities and hospitals. Asthma is also responsible for significant mortality, particularly when not properly treated.

It is generally accepted that asthma is characterized by chronic airway inflammation, varying degrees of airway obstruction which is usually reversible, and increases in airway responsiveness to a variety of stimuli. Muscle spasm, airway edema, abnormal mucous production and an inflammatory cell filtrate can often be observed during an acute exacerbation, frequently referred to by sufferers as "an asthma attack."

Airway edema and bronchospasm usually can be successfully treated with bronchodilators, such as

epinephrine and the β_2-agonists albuterol (also called "salbutamol"), metaproterenol, pirbuterol, terbutaline and salmeterol. Airway narrowing can usually be blocked by administering systemic corticosteroids, such as prednisone, or inhaled anti-inflammatory drugs such as beclomethasone dipropionate, flunisolide, triamcinolone acetonide, cromolyn sodium and nedocromil sodium. The β_2-agonists are used as daily maintenance medications and as "rescue" medications, when they are administered as needed when exacerbated symptoms are experienced. Systemic corticosteroids are given therapeutically, usually in large doses, for treatment of status asthmaticus, while the corticosteroids are prophylactic and are typically administered for the more severe cases in regular, spaced doses regardless of current symptoms. Action of these treatments results in relief from cough, wheezing and the feeling of breathlessness, plus a reduction in airway narrowing which can easily be quantified by measuring improvements in the patient's forced expiratory volume (FEV) or peak expiratory flow (PEF) rate values; the determination and significance of these parameters are discussed at pages 584-599 of R. Berkow, Ed., The Merck Manual of Diagnosis and Therapy, Fifteenth Edition, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey, 1987, particularly at pages 588-9. Some patients further require additional oral, injected and/or inhaled medications to control their disease, the ultimate objective of treatment being to eliminate acute exacerbations.

Studies have shown that about 11 percent of patients with nasal allergy symptoms also suffer from asthma, and that as many as 80 percent of bronchial asthma sufferers may also have allergic rhinitis. Histamine has been implicated as a pathogenic mediator in both upper and lower airway diseases, and studies have been conducted to determine the effect of

histamine H_1 receptor antagonist "antihistamines" on asthma symptoms. With the older drugs, frequently identified as "sedating" antihistamines, their anticholinergic effects were generally found to be detrimental to asthma patients, and it is thus the conventional thought that antihistaminic drugs are contraindicated for asthmatics. Typical advice is that given by J. E. Donnelly et al., "Inadequate Parental Understanding of Asthma Medications," Annals of Allergy, Vol. 62, pages 337-341 (1989) where it is stated at pages 338-9:

> It can be observed that substantial percentages of children had received antibiotics, antihistamines and decongestants for their asthma... These three groups of drugs have no place in the treatment of childhood asthma.

However, the advent of antihistamines having a reduced sedation effect (such as cetirizine) and nonsedating antihistamines (such as terfenadine and loratadine) have renewed interest in treating asthma with antihistamines. It is stated by P. V. Williams et al. in the chapter entitled "Asthma in Children" of R. E. Rakel, ed., Conn's Current Therapy 1995, W. B. Saunders Co., Philadelphia, Pennsylvania, 1995, pages 682-691, at page 686 that:

> *Antihistamines* are weak bronchodilators, and newer agents, many of which are not available in the United States, have some anti-inflammatory properties. They are not as effective as other medications available for the treatment of asthma, and thus do not have a role in routine asthma management. They are mentioned here, however, to counteract the statements found in many package inserts that antihistamines should not be used in

patients with asthma. Their use in patients with upper airway allergies is not contraindicated if the patient has asthma and they may have a beneficial effect on the asthma as well.

Studies performed with the usual allergic rhinitis treatment doses of the reduced sedating antihistamine drug cetirizine include those reported in the following articles: G. Bruttman et al., "Protective Effect of Cetirizine in Patients Suffering from Pollen Asthma," Annals of Allergy, Vol. 64, pages 224-228 (1990); J. H. Dijkman et al., "Prophylactic Treatment of Grass Pollen-Induced Asthma with Cetirizine," Clinical and Experimental Allergy, Vol. 20, pages 483-490 (1990); J. A. Grant et al., "Cetirizine in Patients with Seasonal Rhinitis and Concomitant Asthma: Prospective, Randomized, Placebo-Controlled Trial," The Journal of Allergy and Clinical Immunology, Vol. 95, pages 923-932 (1995); and D. W. Aaronson, "Evaluation of Cetirizine in Patients with Allergic Rhinitis and Perennial Asthma," Annals of Allergy, Asthma and Immunology, Vol. 76, pages 440-446 (1996). It was generally found that cetirizine caused some improvement in asthma symptoms such as chest tightness, wheezing, shortness of breath and cough, together with relief of the rhinitis symptoms. However, no significant improvement in pulmonary function has been shown, as measured by FEV values and other parameters.

Terfenadine has also been studied, as reported by: A. Taytard et al., "Treatment of Bronchial Asthma with Terfenadine; a Randomised Controlled Trial," British Journal of Clinical Pharmacology, Vol. 24, pages 743-746 (1987); P. Rafferty et al., "Terfenadine, a Potent Histamine H_1-Receptor Antagonist in the Treatment of Grass Pollen Sensitive Asthma," British Journal of Clinical Pharmacology, Vol. 30, pages 229-235 (1990); and R. Wood-Baker et al., "A Double-Blind, Placebo

Controlled Study of the Effect of the Specific Histamine H_1-Receptor Antagonist, Terfenadine, in Chronic Severe Asthma," British Journal of Clinical Pharmacology, Vol. 39, pages 671-675 (1995). Twice the usual dose for allergic rhinitis, or 120 milligrams of terfenadine twice daily, had at best a slight positive effect on pulmonary function. However, the dosing regimen used by Rafferty et al., 180 milligrams three times per day, resulted in increased PEF values by 5.5 percent in the morning and 6.2 percent in the evening. Due to the well-known cardiotoxicity potential of this drug, routine administration of abnormally large doses may not be wise.

A. Dirksen et al., "Effect of a Non-Sedative Antihistaminic (Loratadine) in Moderate Asthma," Allergy, Vol. 44, pages 566-571 (1989) reported the results of a study which administered a normal allergic rhinitis treatment dose of loratadine (10 milligrams, once daily) to asthmatics. Patients exhibited a lessening of asthma symptoms with the treatment, but showed only small improvements in pulmonary function which were described as not statistically significant.

Decongestant drugs are often used to treat allergic rhinitis. The most significant of these are sympathomimetic amines having α-adrenergic stimulating activity. Among the more widely used orally delivered agents are phenylpropanolamine, ephedrine and pseudoephedrine. Decongestants have long been used in combination with antihistamines for treating allergic and other forms of rhinitis, and some of the publications discussed above relating to cetirizine and terfenadine studies indicate that patients in the antihistamine clinical studies were allowed to use pseudoephedrine for additional relief of symptoms. However, there is no unexpected benefit attributed to this use.

SUMMARY OF THE INVENTION

The invention encompasses a method for improving pulmonary function of a patient suffering from asthma, comprising administering to the patient the customary rhinitis treatment-effective amounts of loratadine and a decongestant.

A preferred decongestant is pseudoephedrine, and a presently preferred daily treatment for obtaining the desired results of the invention includes 10 milligrams of loratadine and one of: 240 milligrams of pseudoephedrine, administered in a suitable extended release formulation for 24-hour effectiveness; or two daily doses of 5 milligrams of loratadine and 120 milligrams of pseudoephedrine, administered in an extended release formulation for 12-hour effectiveness; or in up to four divided doses of immediate release formulations during 24 hours, totalling 10 milligrams of loratadine and 240 milligrams of pseudoephedrine. Particularly with the immediate release formulations, the individual drugs can be administered separately or in a combination dosage form.

BRIEF DESCRIPTIONS OF THE DRAWINGS

Fig. 1 is a graphical representation of morning PEF data obtained in the clinical test of the example.

Fig. 2 is a graphical representation of evening PEF data obtained in the clinical test of the example.

Fig. 3 is a graphical representation of FEV data obtained in the clinical test of the example.

DETAILED DESCRIPTION OF THE INVENTION

A reference herein to "customary rhinitis-effective treatment amounts" of a drug is intended to indicate those doses which are approved by any relevant regulatory agencies, such as the United States Food and Drug Administration, for use of the drug to treat symptoms of allergic rhinitis. References herein to "improving pulmonary function" are meant to include a facilitation of gas exchange processes in the lungs, particularly as shown clinically by improvements in measured FEV and/or PEF values for a patient; such improvements will usually be accompanied by a reduction in the patient's perception of shortness of breath.

Loratadine, chemically ethyl-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate with an empirical formula $C_{22}H_{23}ClN_2O_2$ and a molecular weight of 382.89, is a very widely used nonsedating antihistamine drug with a superb safety profile. The active drug and its preparation are described in United States Patent 4,282,233 to Vilani. The drug may also conveniently be prepared according to the process described in United States Patent 4,731,447 to Schumacher et al. For purposes of the present invention, loratadine may be administered in any of several dosage forms, including, without limitation, tablets, capsules, syrups or by injection; as with most drugs, oral administration in the form of a tablet or capsule will be preferred for patient convenience.

An effective antihistaminic dose of loratadine ranges from about 5 to about 40 milligrams daily. Due to the systemic half-lives of loratadine and its active metabolites, the daily dose may be given once each 24 hours or divided into 2, 3, or 4 preferably equal portions for administration to match the frequency of decongestant drug dosing. A typical daily dose of

loratadine for relief of the symptoms of allergic rhinitis is 10 milligrams. Schering Corporation of Kenilworth, New Jersey markets a 10 milligram loratadine tablet under the brand CLARITIN®.

Useful decongestant drugs include topical decongestants and systemic decongestants. Topical decongestants are typically administered in the form of drops or aerosols such as nasal sprays, and contain such drugs as oxymetazoline, phenylephrine, naphazoline, xylometazoline, ephedrine, epinephrine, methylhexaneamine, tetrahydrozoline and xylometazoline. Topical decongestants are not preferred for long-term therapy, due to the eventual appearance of rhinitis medicamentosa which can usually be treated only by discontinuing administration of the drug.

Suitable systemic decongestant drug compounds for the practice of the invention include the sympathomimetic amines phenylpropanolamine, ephedrine, pseudoephedrine and phenylephrine, a reference herein to the drug specifically including pharmaceutically acceptable salts thereof, where necessary. The most widely used of these is pseudoephedrine, due to its favorable balance of efficacy and safety; typically, the water-soluble hydrochloride, sulfate or other salts are used to formulate products. Pseudoephedrine sulfate is chemically [S-(R*,R*)]-α-[1(methylamino)ethyl] benzenemethanol sulfate with an empirical formula of $(C_{10}H_{15}NO)_2 \bullet H_2SO_4$ and a molecular weight of 428.54. The extraction of this compound from Ma Huang, and chemical synthesis of the compound, are well known in the art. For purposes of the present invention, pseudoephedrine salts may be administered in any of several dosage forms, including, without limitation, tablets, capsules, syrups or by injection; as with most drugs, oral administration in the form of a tablet or capsule will be preferred for patient convenience.

Typically, pseudoephedrine sulfate or hydrochloride will be administered to adults in daily doses of 120 to 360 milligrams, and to children in daily doses of 60 to 180 milligrams, for the alleviation of congestion from allergic rhinitis. However, the systemic half life of pseudoephedrine is considerably shorter than that of loratadine. In immediate release formulations, individual doses of 60 milligrams are usually administered to an adult patient four times in each 24-hour period. However, a number of extended release solid formulations are known in the art, for example to make 120 milligrams of the drug effective over a 12-hour period, and 240 milligrams effective for a full 24 hours.

It is not essential that the loratadine and decongestant be dosed together. For example, loratadine can be administered once daily, while the decongestant drug is administered more frequently to maintain a therapeutic systemic drug level. Even when the drugs are dosed together, it is not necessary that they are present in the same formulation or dosage form.

Formulations which combine doses of antihistaminic drugs and decongestant drugs are well known in the art. For loratadine, these include a formulation containing 5 milligrams of loratadine and 60 milligrams of pseudoephedrine sulfate for immediate release from a tablet coating, together with 60 milligrams of pseudoephedrine which is released at a controlled rate from an erodible tablet matrix, for providing effectiveness over a 12-hour period; a useful product is commercially available in the United States from Schering Corporation of Kenilworth, New Jersey under the brand CLARITIN-D® 12 HOUR. Another formulation incorporates 10 milligrams of loratadine for immediate release from a tablet coating together with 240 milligrams of pseudoephedrine which is released at a

controlled rate from an erodible tablet matrix, for providing effectiveness over a 24-hour period; this technique is described in United States Patent 5,314,697 to Kwan et al. and a useful product is available in the United States from Schering Corporation under the brand CLARITIN-D® 24 HOUR. Such combination formulations will be preferred by most patients, for convenience.

The invention will be further explained with reference to the following example, which is not intended to limit the scope of the appended claims in any manner.

EXAMPLE

A clinical trial was conducted, in which 193 adult patients suffering from both asthma and rhinitis were randomized to receive either the above-described CLARITIN-D® - 12 HOUR product or a placebo twice daily for six weeks, during the fall allergy season. All of the patients had been using, and continued to use during the study, the bronchodilator drug albuterol from a pressurized aerosol metered dose inhaler as prescribed by physicians to control asthma symptoms. No other rhinitis or asthma medications were permitted to be used by the patients during the study.

Patients were evaluated prior to commencement of the study by, *inter alia*, FEV and PEF rate measurements to generate baseline data, and the evaluations were repeated weekly during the study.

Patients receiving the combination of drugs were found to experience a marked reduction of both rhinitis and asthma symptoms, as compared to the patients receiving only placebo.

Fig. 1 shows results from morning measurements of PEF rates for patients receiving loratadine and pseudoephedrine sulfate (solid line) and placebo

(broken line). The ordinate is the mean change of PEF rate from baseline values, expressed in liters per minute. There was a very clear, statistically significant improvement during the study due to the drug combination administration.

Fig. 2 is a similar representation of results from an evening measurement of PEF rates for the patients, the groups being identified as above. The similar clear, statistically significant improvement during the study is a result of the drug combination administration.

Fig. 3 is a representation of further study results, as generated by measurements of FEV in the first second ("FEV_1"). The ordinate shows mean change from baseline FEV_1 values, expressed in liters. Data from patients receiving loratadine and pseudoephedrine sulfate are identified by the solid bar, while data from patients receiving only placebo are represented by the open bar. The very clear, statistically significant improvement in pulmonary function during the study is due to the drug combination administration.

The magnitude of improvements in pulmonary function shown herein will be important for the well-being of an asthmatic patient, regardless of whether or not the patient suffers from rhinitis.

WHAT IS CLAIMED IS:

1. A method for improving pulmonary function of a patient suffering from asthma, comprising administering to the patient customary rhinitis treatment-effective amounts of loratadine and a decongestant.

2. The method of claim 1, wherein the decongestant is selected from the group consisting of phenylpropanolamine, ephedrine, phenylephrine, pseudoephedrine or a combination thereof.

3. The method of claim 1, wherein the decongestant comprises pseudoephedrine.

4. The method of claim 3, wherein pseudoephedrine is administered in an amount about 60 to about 360 milligrams per day.

5. The method of claim 3, wherein pseudoephedrine is administered in an amount about 120 to about 240 milligrams per day.

6. The method of claim 1, wherein loratadine is administered in an amount about 5 to about 40 milligrams per day.

7. The method of claim 1, wherein loratadine is administered in an amount about 10 milligrams per day.

8. The method of claim 1, comprising administering 10 milligrams of loratadine daily and about 120 to about 240 milligrams of pseudoephedrine daily.

9. The method of claim 1, wherein the loratadine and decongestant are administered in separate formulations.

10. The method of claim 1, wherein the loratadine and decongestant are combined in a single formulation.

11. A method for improving pulmonary function of a patient suffering from asthma, comprising daily administration to the patient of about 5 to about 40 milligrams of loratadine and about 60 to about 360 milligrams of pseudoephedrine.

12. The method of claim 11, wherein the loratadine and the pseudoephedrine are administered in separate formulations.

13. The method of claim 11, wherein the loratadine and pseudoephedrine are combined in a single formulation.

14. The method of claim 11, wherein loratadine and pseudoephedrine are present in a single tablet formulation in which the loratadine and a portion of the pseudoephedrine are present in a coating, and the remaining pseudoephedrine is present in an erodible matrix.

15. The method of claim 11, wherein loratadine and pseudoephedrine are present in a single tablet formulation in which the loratadine is present in a coating, and the pseudoephedrine is present in an erodible matrix.

16. A method for improving pulmonary function of a patient suffering from asthma, comprising daily administration to the patient of about 10 milligrams of loratadine and about 240 milligrams of pseudoephedrine.

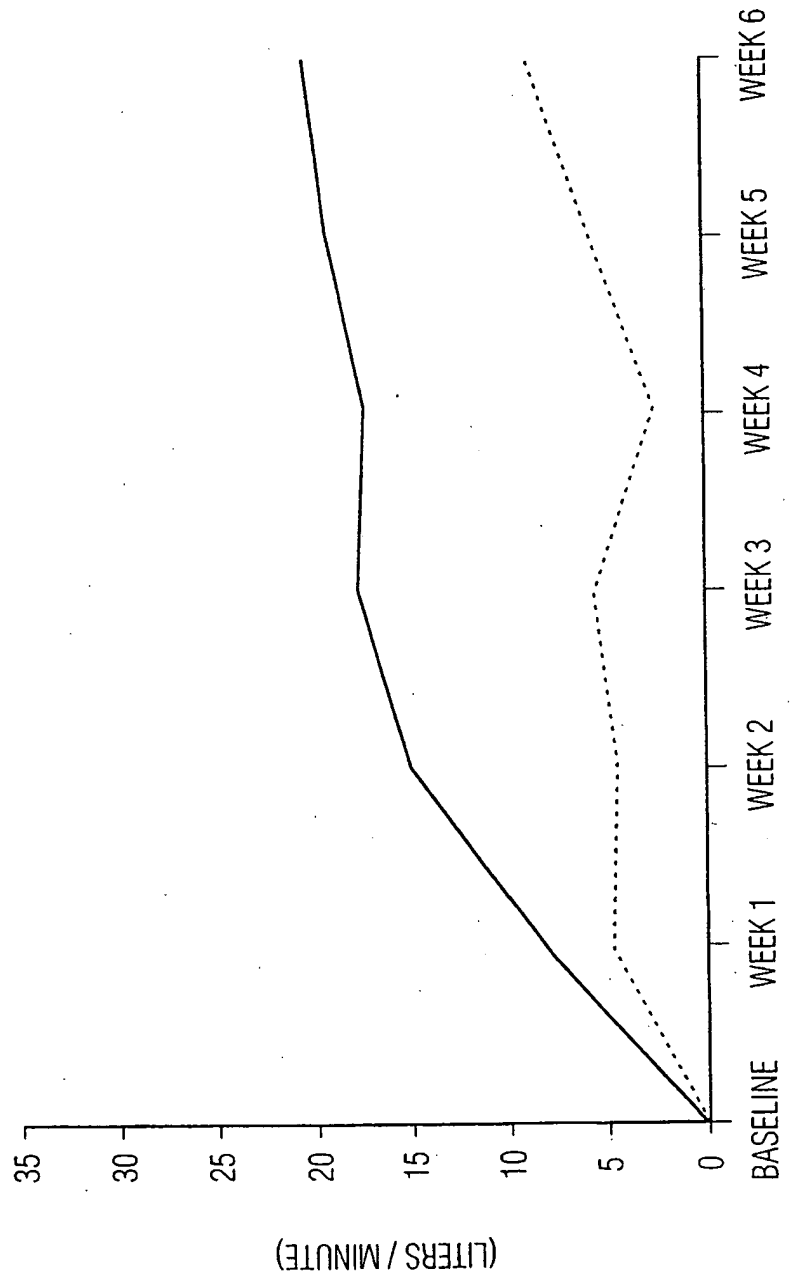
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FIG. 1

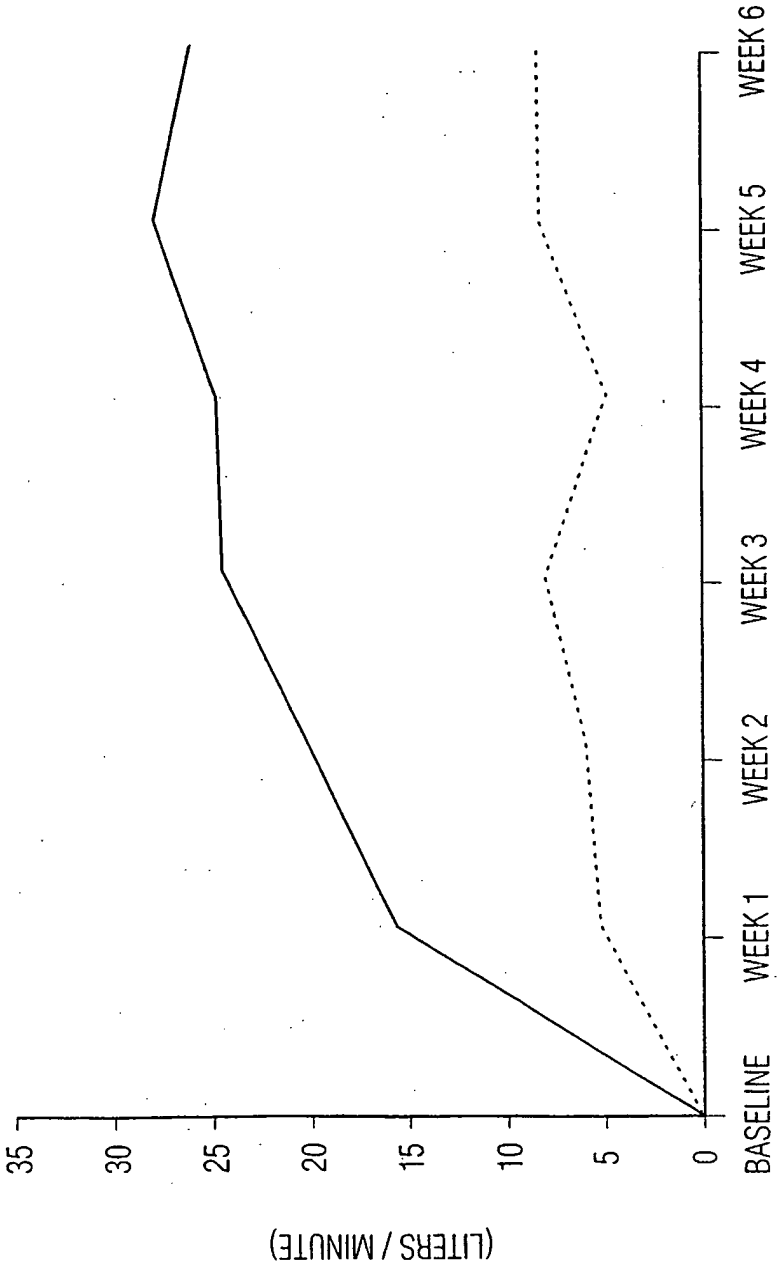
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FIG. 2

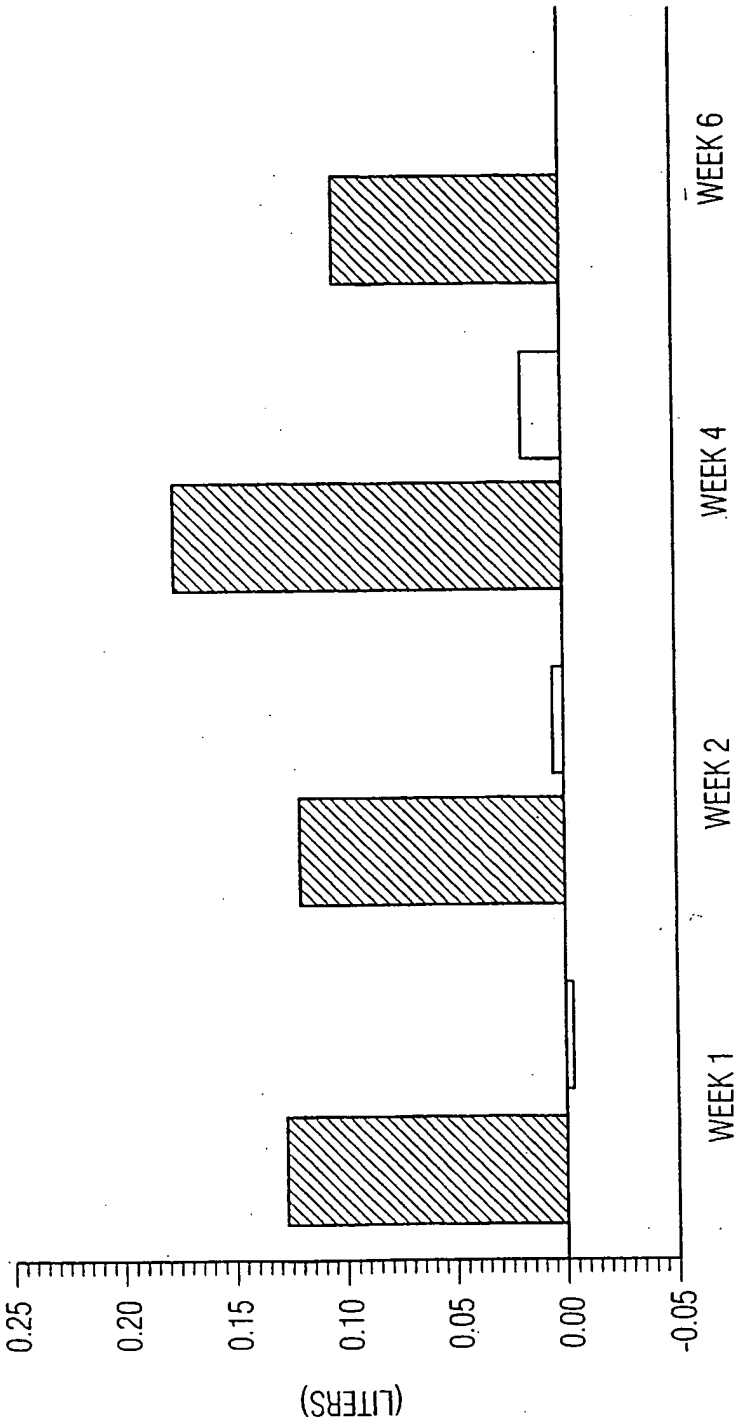

FIG. 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/19158

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445 //(A61K31/445,31:135)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 09761 A (SCHERING CORP ;KWAN HENRY K (US); LIEBOWITZ STEPHEN M (US)) 11 May 1994 see abstract ---	1-16
A	EP 0 396 404 A (SCHERING CORP) 7 November 1990 see claim 1 ---	1-16
A	US 5 407 686 A (PATEL SATISHCHANDRA P ET AL) 18 April 1995 see column 1, line 34-40 ---	1-16
A	WO 96 20708 A (ABERG A K GUNNAR ET AL) 11 July 1996 see line 37-46 --- -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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1

Date of the actual completion of the international search
3 February 1998

Date of mailing of the international search report
18.02.98

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1 110 397 A (MEAD JOHNSON & CO) 18 April 1968 see page 1, column 1, line 26-36	1-16

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/19158

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 97/19158

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Remark : Although claims 1-16 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the composition.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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